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Synthesis of Two Key Fragments of the Complex Polyhalogenated Marine Meroterpenoid Azamerone

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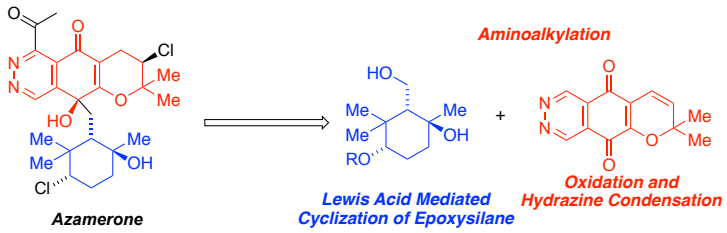
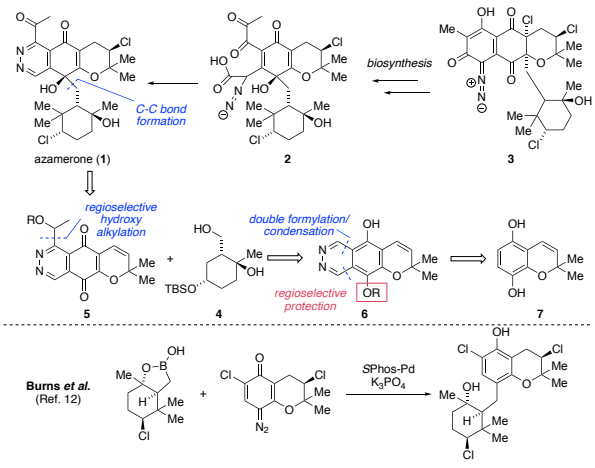


ABSTRACT: A concise route towards two advanced fragments in the context of the total synthesis of the unique natural product azamerone is reported. Key synthetic features include the enantioselective synthesis of an epoxysilane and its Lewis acid induced cyclization and the installation of the pyridazine ring via a formylation/condensation sequence. This route provides strategic insights into the chemistry of phtalazinediols, facilitating synthetic approaches towards this class of natural products.

Over the last years, marine-sediment derived bacteria of the order of Actinomycetales (= actinomycetes) have been recognized as a valuable source for the discovery of novel, structurally unique natural products with interesting biological activity,[1,2] such as antibacterial,[2] anticancer[3] and anti-infective[4] properties. As an example of this chemical diversity, these organisms are producing a family of halogenated natural products called napyradiomycins, of which there are over 40 known members.[5] Surprisingly, only the total synthesis of one member of this class, namely napyradiomycin A1, has been reported,[6] and very recently, Moore and co-workers published the total enzyme synthesis of napyradiomycins A1 and B1.[7] In 2006, Fenical and co-workers isolated a new member of this class, which could be identified as the unusual meroterpenoid phtalazinone azamerone (**1**).[8] Besides pyridazomycin, azamerone (**1**) constitutes the only natural product containing a pyridazine-ring, making it a very interesting target for total synthesis within this family of natural products.[9] In contrast to the biosynthesis of pyridazomycin,[9] in which the N–N bond has been suggested to be formed through the cyclization of L-ornithine, the group of Moore could provide evidence that this is not the case for azamerone (**1**).[10] Isolation of co-produced polyhalogenated meroterpenoids and analogues containing a diazo-functionality (**2**, **3**) strongly suggest that the N–N bond in azamerone (**1**) is formed via an oxidative rearrangement of the diazo-functionality of compound **3**.[10] This could be verified by ^{15}N and ^{13}C labelling studies.[10]

Scheme 1. Biosynthesis & Retrosynthetic Analysis.



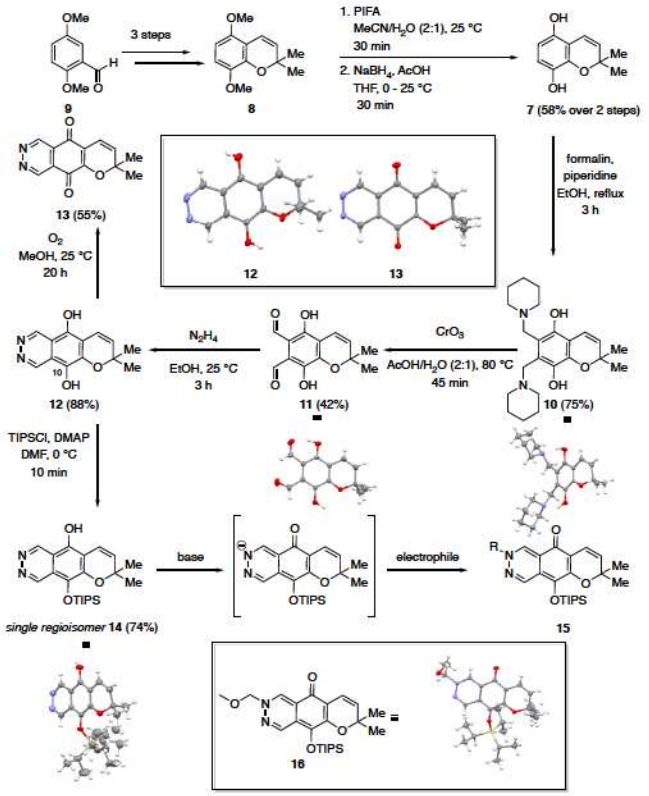
In the context of our interest in N–N bond containing natural products,[11] the structurally unique phtalazinone core of azamerone (**1**), the interesting halogenation pattern, and the highly functionalized cyclohexane side-chain, we selected this unique natural product as a challenging target for total synthesis.

Our retrosynthesis of azamerone (**1**) aimed at disconnecting the bond between cyclohexane unit **4** and the tricyclic phtalazinedione **5**, which we envisioned to install late stage via a metal–mediated C–C bond-forming reaction (Scheme 1). Interestingly, Burns and co-workers recently and independently disclosed a similar strategy by employing a cyclic boronic hemiester and an azoquinone, which successfully lead to the total synthesis of azamerone (**1**).[12] The acetyl side-chain of azamerone (**1**) would be installed via a protecting group directed, regioselective lithiation of the pyridazine-ring of tricycle **6** followed by trapping with aldehyde, to produce tricyclic structure **5**. The pyridazine ring in turn would be formed by a double formylation followed by a condensation, which leads

to bicycle 7 as a suitable starting material for our synthetic endeavors.

Our synthesis of key bicyclic hydroquinone 7 (Scheme 2) started with a three step sequence,[13] which delivered protected intermediate **8** in high yield from commercially available 2,5-dimethoxybenzaldehyde (**9**). Unfortunately, deprotection of the methyl-groups under standard conditions (BBr_3, BCl_3, $AlCl_3$) led only to decomposition.[14]

Scheme 2. Synthesis of the core structure of azamerone (1).

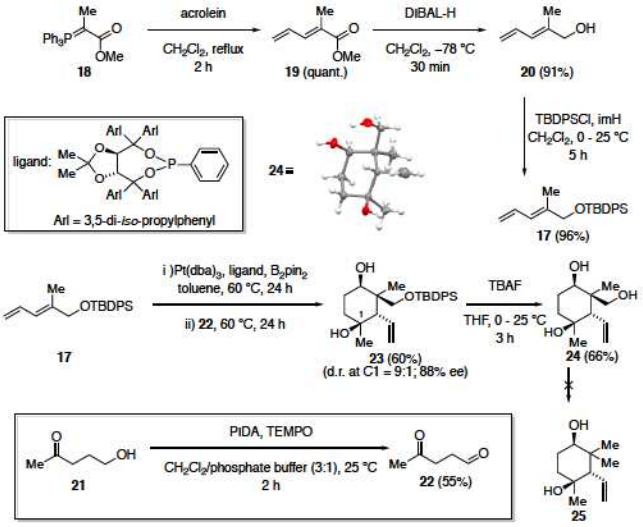


However, oxidative demethylation using [bis(trifluoroacetoxy)iodo]benzene (PIFA) in acetonitrile/water (2:1, v/v) afforded the corresponding para-quinone in good yield.[15] Subsequent reduction using *in situ* generated sodium triacetoxyborohydride afforded hydroquinone 7 in 89% yield. With this intermediate in hand, we set out to investigate the key three step sequence for installing the pyridazine-ring of the natural product. Upon treatment of hydroquinone 7 with piperidine and aqueous formaldehyde solution, the desired diaminoalkylation was observed, delivering compound **10** in 75% yield.[16] The reaction of **10** in acetic acid with a solution of chromium(VI) oxide in acetic acid/water (1:1, v/v) furnished desired diformyl dihydroquinone **11**.[17] Ring closure was then affected by condensation with hydrazine hydrate, which led to pyridazine core structure **12** in 88% yield. However, tricycle **12** proved to be prone to oxidation, which leads to the formation of quinone **13** in trace amounts upon column chromatography. Full conversion to intermediate **13** was observed after 20 h under an oxygen atmosphere.

With these promising results in hand, we set out to investigate the introduction of the acetyl side-chain. Regioselective protection of the hydroxy-group at position C-10 of tricycle **12** proved to be challenging due to decomposition of the product in the reaction mixture. After extensive experimentation, suitable conditions were identified, which involved a large excess (10 equiv) of tri-*iso*-propylsilyl chloride (TIPSCl) and 4-(dimethylamino)pyridine (DMAP) as a catalyst and base, which furnished the desired regioisomer **14**, as unambiguously shown by X-ray crystallography, in 74% yield.

However, when treating the mono-TIPS protected hydroquinone **14** with a base (NEt_3, NaH, LiHMDS, K_2CO_3) followed by an electrophile (MOMBr, MEMCl, Me_3OBF_4) dearomatization was observed, leading to the sole isolation of dearomatized, nitrogen-protected compounds of the general structure **15** in up to 50% yield on 10 mg scale. The structure was confirmed by X-ray analysis of the MOM protected tricycle **16** (Scheme 2). Increasing the scale to 50 mg resulted in a drastic drop in yield and additionally, migration of the TIPS group could be observed in trace amounts.

Scheme 3. Tandem diborylation-double allylation.

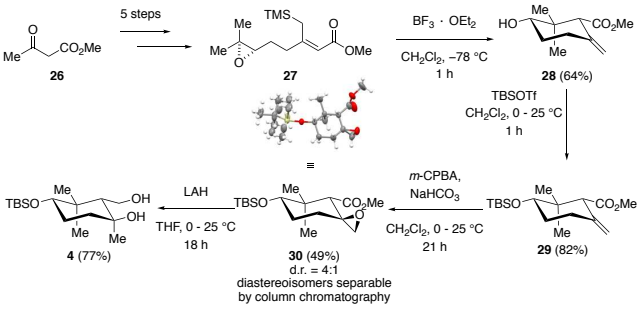


In parallel, we turned our attention to the enantioselective synthesis of the cyclohexane unit of azamerone (**1**). Previously, Snyder and co-workers developed a chloronium-induced cyclization method for the synthesis of a precursor of the cyclohexane unit.[18,19] However, this reaction delivered only racemic material, rendering a tedious separation via resolution mandatory.[18] Thus, our first approach sought to employ the enantioselective, catalytic diborylation-double allylation strategy developed by the group of Morken.[20]

To explore the feasibility of this approach, we synthesized diene **17** in three steps from phosphorous ylide **18**.[21] Wittig olefination with acrolein furnished diene **19**, which could be reduced to primary alcohol **20** using DIBAL-H.[21] Protection of the primary hydroxy group with *tert*-butyl(chloro)diphenylsilane (TBDPSCl) then furnished silyl ether **17**. Oxidation of 5-hydroxy-2-pentanone (**21**) using (diacetoxyiodo)benzene (PIDA) and (2,2,6,6-tetramethylpiperidin-1-yl)oxyl (TEMPO) afforded dicarbonyl **22**.[20] We then turned our attention to the key tandem diborylation-double allylation reaction. Gratifyingly, the enantioselective Pt-catalyzed diboration of diene **17** with bis(pinacolato)diboron (B_2pin_2) using $Pt(dba)_3$ as a catalyst and a TADDOL-derived ligand, followed by *in situ* trapping of the diborylated species with dicarbonyl **22** delivered cyclohexane **23** in 60% yield with a d.r. of 9:1 (as judged by ^{1}H-NMR at position C1) (Scheme 3) and 88% ee. The relative

configuration was validated by deprotection of the silyl ether by using TBAF to afford triol **24**, from which a suitable crystal for an X-ray crystal structure determination could be obtained. With these results, we set out to explore the deoxygenation of the primary hydroxy-group. However, even after employing a large variety of conditions, this was not successful. Instead of the formation of the desired compound **25**, the main byproducts observed included oxetane formation (I_2, PPh_3, imH), or thiocarbonate formation (TCDI, NEt_3, DMAP), when trying to install a thiocarbonylimidazole precursor for radical deoxygenation. Based on these results we decided to focus on a different strategy, which utilizes the Lewis acid induced cyclization of epoxysilanes (Scheme 4).

Scheme 4. Enantioselective synthesis of cyclohexane unit.



Starting from methyl acetoacetate (**26**), epoxysilane **27** could be prepared in an enantiomerically enriched form in five linear steps.[22] Upon treatment with boron trifluoride etherate, the Lewis acid induced cyclization of epoxide **27** could be achieved to give cyclohexane **28**.[22] TBS-protection of the secondary hydroxy group furnished silyl ether **29**. This group was envisioned to shield the back face of compound **4**, thus enhancing the diastereoselectivity in the key C–C bond formation to the tricyclic core of azamerone (**1**). Epoxidation using *m*-CPBA and sodium bicarbonate afforded a 4:1 mixture of diastereomers, favoring the desired epoxide **30**, which was verified by X-ray crystallography after separation of the diastereomeric mixture. Finally, global reduction of epoxide **30** afforded diol **4**. This cyclohexane-unit has all required stereocenters in place and can be seen as a suitable partner for coupling with the core structure of azamerone (**1**), for example via a similar strategy to that employed by the Burns group.[12]

Herein we report the successful synthesis of two advanced fragments, which can be utilized in the total synthesis of azamerone (**1**). The synthesis relies on the cyclization of epoxysilane **27** and the rapid synthesis of the tricyclic core of the natural product via an aminoalkylation-oxidation-condensation sequence. In contrast to previous methods reported for the synthesis of the cyclohexane unit, the cyclization of epoxysilanes such as **27** establishes an enantioselective approach to the complex substitution pattern of the side chain of azamerone (**1**).

ASSOCIATED CONTENT

Supporting Information

Experimental details, analytical data (^{1}H-NMR, ^{13}C-NMR, MS, IR, melting points for solids, as well as chiral HPLC traces) are included in the Supporting Information. Crystallographic data for compounds **10**, **11**, **12**, **13**, **14**, **16**, **24** and **30** are also included therein.

The Supporting Information is available free of charge on the ACS Publications website.

Accession Codes

CCDC-1886619–1886625 and 1890051 contain the supplementary crystallographic data for this paper. The data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/structures.

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Notes

The authors declare no competing financial interest.

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